



Assessment of tumour control probability and equivalent uniform dose in conventional 3D-CRT vs. hypo-fractionated IMRT

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Keywords

Conventional fractionation;
Equivalent Uniform Dose (EUD);
Hypo-fractionation;
Prostate cancer;
Tumour Control Probability (TCP)

Abstract

Hypo-fractionated (HF) radiotherapy offers a promising solution to improve access to cancer treatment in resource-limited settings, such as developing countries, by reducing the number of treatment sessions compared to conventional fractionation (CF). For effective implementation, evaluating Equivalent Uniform Dose (EUD) and Tumour Control Probability (TCP) is essential to ensure treatment efficacy across different radiotherapy techniques. This study compares treatment plans generated using Three-Dimensional Conformal Radiation Therapy with Conventional Fractionation (3D-CRT CF) and Intensity Modulated Radiation Therapy with Hypo-fractionation (IMRT HF) in patients with localized prostate cancer. A total of 50 patients were CT-simulated, and their images were imported into a Treatment Planning System (TPS). Planning Target Volume (PTV) and Organs at Risk (OARs) were delineated. Both IMRT HF and 3D-CRT CF plans were generated using identical CT datasets and isocenter positioning. Cumulative Dose Volume Histograms (DVHs) were extracted, and EUD and TCP values were computed using the EUD program. The mean EUD for IMRT HF was 60.7 ± 2.63 Gy (97.92% of the prescribed dose), while for 3D-CRT CF, it was 71.58 ± 4.8 Gy (96.73% of the prescribed dose). Mean TCPs were $90.4 \pm 4.61\%$ and $95.6 \pm 5.52\%$ for IMRT HF and 3D-CRT CF, respectively. Results indicate comparable tumour control, with 3D-CRT CF showing slightly higher TCP.

Introduction

Tumour Control Probability (TCP) is a key radiobiological metric used to assess the effectiveness of radiotherapy in eradicating

cancer cells, while Normal Tissue Complication Probability (NTCP) quantifies the risk of radiation-induced toxicity in normal tissues and organs at risk (Mesbahi et al.

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2019). Achieving high TCP depends on multiple factors, including dose per fraction, total dose, fractionation schedule, treatment technique, tissue characteristics (e.g., α/β ratio), and biological responses such as repair and repopulation (Rany Nuraini and Rena Widita 2019).

Although different techniques may deliver the same prescribed dose, variations in dose distribution due to anatomical inhomogeneities and delivery methods can significantly influence treatment outcomes (Chopra et al. 2018). For example, Intensity Modulated Radiation Therapy (IMRT) can provide superior dose conformity to irregularly shaped targets such as the prostate compared to Three-Dimensional Conformal Radiation Therapy (3D-CRT) (Wu et al. 2002).

This study compares two radiotherapy regimens for the treatment of localized prostate cancer: conventional fractionation (CF), delivering 74 Gy in 2 Gy fractions using 3D Conformal Radiotherapy (3D-CRT), and hypofractionation (HF), delivering 62 Gy in 3.1 Gy fractions using Intensity-Modulated Radiotherapy (IMRT). Both regimens were designed to deliver a comparable Biological Effective Dose (BED), accounting for tissue-specific radiosensitivity. To assess their clinical effectiveness, it is essential to compare Equivalent Uniform Dose (EUD) and Tumor Control Probability (TCP) between the two techniques before the widespread clinical adoption of hypofractionation in the country.

While modern dose calculation algorithms such as the Anisotropic Analytical Algorithm (AAA) provide accurate dose distributions, they are limited in directly predicting clinical outcomes due to inherent technological constraints (de Martino et al. 2021). Therefore, this study evaluates routine 3D-CRT CF and IMRT HF treatment plans implemented at the Ocean Road Cancer Institute (ORCI) as part of

the Hypo-Africa Clinical Trial. An independent EUD-based radiobiological model was used to estimate TCPs and provide a comparative analysis of the two planning strategies, aiming to support evidence-based decision-making in prostate cancer radiotherapy.

Materials and Methods

Selection of Patients

A total of 50 patients with histologically confirmed localized prostate cancer were recruited for this study. Patient selection was independent of tumour size, Prostate-Specific Antigen (PSA) levels, or Gleason score, allowing for a diverse sample reflective of typical clinical presentations.

However, patients with radiological evidence of pelvic nodal involvement were excluded to avoid the complexity of extending the treatment field to the pelvic lymph nodes. This exclusion ensured uniformity in treatment volume and planning, as illustrated in Figures 1(a) and (b). Figure 1(a) demonstrates the dose distribution achieved with an IMRT hypo-fractionated (HF) plan, showing a uniform dose within the Planning Target Volume (PTV) while effectively sparing the upper rectum and lower bladder. In contrast, Figure 1(b) shows the 3D-CRT conventional fractionation (CF) plan, where both the upper rectum and lower bladder receive higher doses, indicating less organ sparing.

Additional exclusion criteria included patients with distant metastases (confirmed by bone scintigraphy), prior pelvic radiotherapy, bilateral hip prostheses, or previous prostatectomy. These factors were excluded due to their potential to compromise dose calculation accuracy in the Treatment Planning System (TPS) and to ensure the feasibility of applying a consistent field size across both radiotherapy techniques.

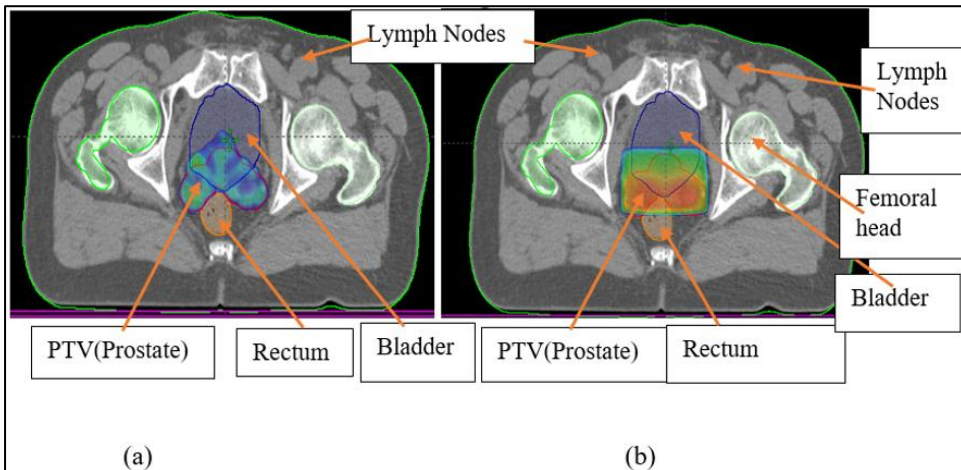


Figure 1: Dose distribution of the Prostate Plan (a) IMRT HF and (b) 3D-CRT CF.

Computed Tomography Scanning Preparation for CT Simulations

Prior to CT simulation, all selected patients underwent a standardized preparation protocol to ensure consistent bladder and rectal conditions. Patients were instructed to empty their bladders approximately one hour before the scan, followed by emptying their rectums of flatus and fecal matter. Subsequently, each patient was asked to drink approximately 300 ml of water to adequately fill the bladder, aiding in its displacement from the Planning Target Volume (PTV) and reducing radiation exposure to surrounding organs at risk.

CT image acquisition was performed using a Siemens Healthineers Somatom Confidence CT simulator with a slice thickness of 5 mm. For prostate cancer simulation, patients were positioned in the supine position, head-first into the scanner bore.

To minimize patient movement and ensure reproducibility throughout both simulation and treatment delivery, appropriate positioning and immobilization devices were utilized. These included customized supports and alignment tools, which were consistently applied during both the planning and treatment phases to enhance setup accuracy and treatment precision.

Contouring and Radiation Treatment Planning

CT images for each patient were acquired and imported into the Eclipse Treatment Planning System (Version 15.1). Contouring

of the Gross Tumour Volume (GTV), Clinical Target Volume (CTV), and Planning Target Volume (PTV) was performed by a qualified Radiation Oncologist (RO), following the guidelines provided in ICRU Reports No. 62 and 83. Organs at Risk (OARs), including the bladder, rectum, penile bulb, and femoral heads (as shown in Figure 1), were also delineated, although OAR outcomes are not presented in this study.

Two radiation treatment plans were developed for each patient using the same contoured CT dataset; IMRT Hypofractionated (HF) plan: 3.1 Gy per fraction over 20 fractions, totaling 62 Gy (delivered five days per week). 3D-CRT Conventional Fractionation (CF) plan: 2 Gy per fraction over 37 fractions, totaling 74 Gy (also delivered five days per week).

Both plans used a 6 MV photon beam energy and the Anisotropic Analytical Algorithm (AAA) for dose calculation. For IMRT optimization, the Photon Optimizer algorithm was applied. Gantry angles for IMRT plans were set at 0°, 52°, 104°, 156°, 208°, 260°, and 312°. For 3D-CRT CF plans, a four-field technique with gantry angles at 0°, 90°, 180°, and 270° was used.

In the 3D-CRT CF plans, Multi-leaf Collimators (MLCs) were adjusted to conform the radiation dose to the PTV. For both techniques, cumulative and differential Dose Volume Histograms (DVHs) were generated, presenting absolute dose (Gy) and volume

(cm³). These DVHs were used to calculate the Equivalent Uniform Doses (EUDs) and Tumour Control Probabilities (TCPs).

Radiobiology Modelling

This study compared two radiotherapy dose regimens: conventional fractionation, delivering 2 Gy per fraction to a total dose of 74 Gy, and hypo-fractionation, delivering 3.1 Gy per fraction to a total dose of 62 Gy. In radiobiology, two regimens are considered biologically equivalent when they yield comparable Biological Effective Dose (BED) values. BED serves as a more accurate indicator of the true biological impact of a treatment, accounting for both the total dose and the dose per fraction, relative to a tissue-specific $\alpha\beta$ ratio.

In this analysis, assuming an $\alpha\beta$ ratio of 3 Gy (commonly used for prostate cancer), the calculated BEDs for the conventional and hypo-fractionated regimens were 124 Gy₃ and 126 Gy₃, respectively. These values were computed using Equation 1, as described by (Dale 1996) and (G.W.Barendsen 1982), confirming that the two regimens are radiobiologically comparable.

$$BED = nd\left(1 + \frac{d}{\alpha/\beta}\right) \quad (1)$$

where *BED* is the Biological Effective Dose, *n* is the number of fractions, *d* is the dose per fraction, and $\alpha\beta$ is an Alpha-Beta ratio which quantifies fractionation sensitivity of the tissue

The subscript 3 in the unit of BED values Gy₃ indicates that an $\alpha\beta$ ratio of 3 Gy was used, which is typically assumed for prostate cancer. To compute the Equivalent Uniform Dose (EUD) and the corresponding Tumour Control Probability (TCP), an independent EUD model-based program was employed. This model uses Dose Volume Histogram (DVH) data extracted from the Treatment Planning System (TPS), as described by (Gay and Niemierko 2007)

Niemierko proposed a phenomenological model that integrates both the DVH and the biological characteristics of the tissue or structure being evaluated. This model condenses the heterogeneous dose distribution into a single biologically equivalent uniform

dose value. The mathematical formulation of the EUD model is provided in Equation 2 (Gay and Niemierko 2007)

$$EUD = \left(\sum_{i=1} (V_i D_i^a) \right)^{\frac{1}{a}} \quad (2)$$

where *a* is a unit-less model parameter that is specific to the normal structure or tumor of interest, and *V_i* is a unit-less parameter representing the partial volume receiving dose *D_i*. The *D_i* and *V_i* data pairs are obtained from the cumulative DVH from a given radiotherapy plan. In this work, the cumulative DVH was obtained from IMRT HF and 3D-CRT CF planning techniques.

To calculate the TCP, the EUD was substituted in the logistic function given by Equation 3 (Gay and Niemierko 2007).

$$TCP = \frac{1}{1 + \left(\frac{TCD_{50}}{EUD} \right)^{4\gamma_{50}}} \quad (3)$$

where γ_{50} and TCD₅₀ are key radiobiological parameters used in assessing prostate cancer response to radiotherapy. TCD₅₀ refers to the Tumour Control Dose required to achieve control in 50% of tumors when the target is homogeneously irradiated. The (γ_{50}), (Gamma-50) is a dimensionless parameter that characterizes the steepness of the dose-response curve and is specific to the tissue or tumor type (Gay and Niemierko 2007)

Dose coverage data in CSV format were extracted from the DVHs of both 3D-CRT CF and IMRT HF plans for further analysis. The $\alpha\beta$ ratio, a tissue-specific parameter from the linear-quadratic model, was used in calculating TCPs. It quantifies the fractionation sensitivity of the irradiated tissue (Ruiz and Feng 2018). The complete set of radiobiological parameters employed for EUD and TCP calculations is summarized in Table 1.

This method was adopted because the Anisotropic Analytical Algorithm (AAA), commonly used in TPS for dose calculation, does not support direct TCP computation due to inherent technological limitations (de Martino et al. 2021).

Table 1: The values of the parameters used in TCP calculations.

Parameter	a	γ_{50}	$TD_{50}(\text{Gy})$	$TCD_{50}(\text{Gy})$	$\alpha/\beta (\text{Gy})$
PTV	10	2	-	46.29	3

Results and Discussion

PTV Dose Coverage

The dosimetric results presented in Figures 2(a), 2(b), and 2(c) demonstrate that both hypo-fractionated (HF) and conventional fractionation (CF) regimens can achieve the required 95% dose coverage of the Planning Target Volume (PTV), independent of the planning technique employed. This confirms the clinical feasibility of both IMRT HF and 3D-CRT CF in treating localized prostate cancer.

Figure 2(a), generated using the Eclipse Treatment Planning System, shows the cumulative Dose Volume Histogram (DVH), which represents the volume of tissue receiving at least a specified dose. The planning acceptance criterion, that a minimum of 95% of the PTV should receive at least 95% of the prescribed dose, is visibly met for both techniques. In contrast, Figure 2(c) displays the differential DVH, illustrating the distribution of volume across specific dose levels. A sharp peak near the prescription dose (62 Gy for IMRT and 74 Gy for 3D-CRT) signifies high conformity and consistent dose delivery to the PTV.

Furthermore, Figure 2(b), plotted using MATLAB software, mirrors the cumulative DVH shown in Figure 2(a). The agreement between the graphs affirms the reliability of the data across different analysis platforms.

On average, the 50 patients analyzed received 97.92% of the prescribed dose with IMRT HF and 96.73% with 3D-CRT CF, confirming uniform dose distribution within the PTV for both techniques, an essential prerequisite for tumor control. However, subtle differences in dose conformity were observed. The 3D-CRT plan exhibited a more noticeable kink in the DVH, suggesting that a larger volume of normal tissue received a dose near the prescription level. This is indicative of lower conformity compared to IMRT, which is inherently more precise due to its modulated beam shaping.

Additionally, the lower dose regions observed in both techniques reflect dose buildup, scatter, and attenuation through organs at risk (OARs) and surrounding healthy tissues before reaching the target. These low-dose volumes, although unavoidable, contribute to the heterogeneity in dose distribution and are more pronounced in 3D-CRT than in IMRT. Notably, the DVH curves for IMRT HF begin to decline around 60 Gy, while those for 3D-CRT CF decline after 70 Gy, corresponding with their respective prescription doses. This further validates the planned dose delivery and supports the accuracy of the radiobiological modeling used in this study.

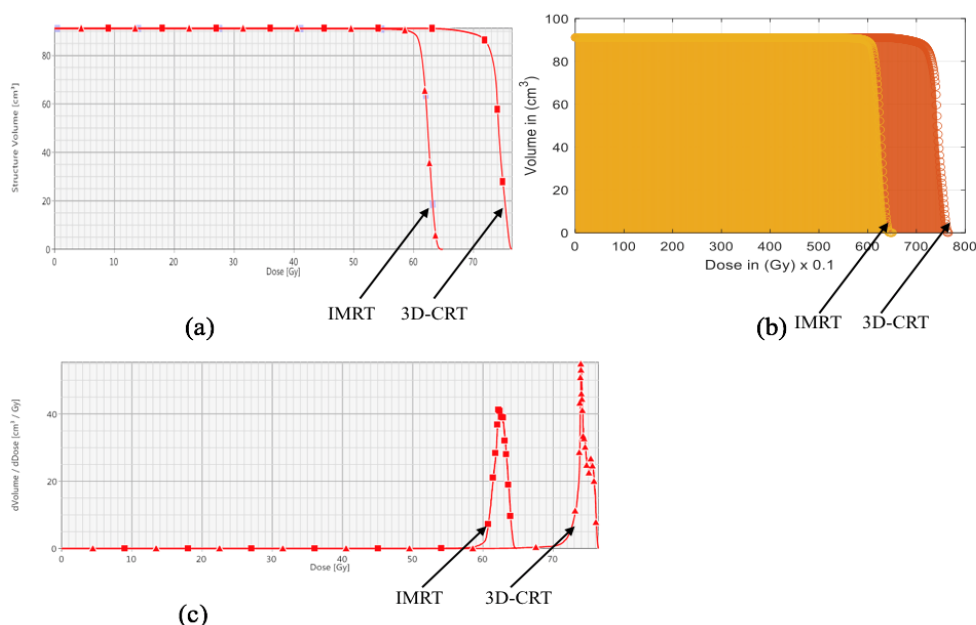


Figure 2: (a) Cumulative DVH of PTV(Prostate) from the TPS showing dose coverage from the two techniques, (b) Cumulative DVH of PTV(Prostate) plotted using Matlab, showing the dose coverage by both techniques, and (c) Differential DVH of PTV(Prostate) from the TPS, the volume that received the prescribed dose for both techniques.

The results presented in Figure 2 indicate that for localized prostate cancer treated without field extension, both planning techniques, 3D-CRT and IMRT, achieved mean dose coverage that met the recommended criteria of delivering at least 95% of the prescribed dose to 95% of the PTV, in accordance with the International Commission on Radiation Units and Measurements (ICRU) Reports 62 and 83 (Grégoire et al. 2004). This consistency underscores the clinical adequacy of both modalities in standard prostate treatment settings.

These findings are aligned with the earlier work by (Luxton et al. 2004), who reported comparable dose coverage between 3D-CRT and IMRT in local field irradiation (LFI) for prostate cancer. However, dose coverage may be compromised when anatomical constraints, particularly the proximity of the rectum and bladder, necessitate stricter protection of organs at risk (OARs).

Notably, 3D-CRT plans tend to provide lower dose coverage in scenarios where OAR

sparing is prioritized. This is due to the inherent limitations of the technique's geometric beam shaping. In 3D-CRT, protection of OARs is primarily achieved by manually adjusting or closing the Multi-Leaf Collimator (MLC) leaves in regions where the PTV and OARs intersect, which often results in under-dosing portions of the PTV adjacent to critical structures.

When treatment fields extend beyond the borders of the high-risk PTV region and encroach upon OARs, manual MLC adjustment becomes necessary to comply with dose constraints. While this approach reduces exposure to normal tissues, it also compromises the conformity and homogeneity of PTV dose coverage in 3D-CRT compared to IMRT. In contrast, IMRT utilizes inverse planning and dynamic MLC movement, enabling superior dose modulation around complex anatomical structures. This results in more conformal plans that maintain target coverage while sparing adjacent organs more effectively, highlighting its advantage in

scenarios with overlapping or closely situated OARs.

Equivalent Uniform Dose

The analysis of Equivalent Uniform Dose (EUD) for the Planning Target Volume (PTV) across all 50 patients revealed high conformity to the prescribed doses in both treatment regimens. For the IMRT hypofractionation

(HF) plan with a prescribed dose of 62 Gy, the mean EUD was (60.7 ± 2.63) Gy, corresponding to 97.92% of the intended prescription. In comparison, for the 3D-CRT conventional fractionation (CF) plan with a prescribed dose of 74 Gy, the mean EUD was (71.58 ± 4.89) Gy, representing 96.73% of the prescribed dose (Table 2).

Table 2: Equivalent Uniform Doses (Gy).

Technique	3D-CRT CF (2 Gy/37/74 Gy)	IMRT HF (3.1Gy/20/62 Gy)
Statistics	71.58 (54.41-75.24, 4.89)	60.71 (50.25-63.81, 2.63)
PTV: EUD (Gy)	Mean (Min-Max, Std dev)	Mean (Min-Max, Std dev)

The results presented in Table 2 show a significant correlation between the Equivalent Uniform Dose (EUD) values obtained from the 3D-CRT conventional fractionation (CF) and IMRT hypofractionation (HF) techniques. A Pearson two-tailed correlation test yielded a p-value of 0.04, indicating that the correlation is statistically significant ($p < 0.05$). This suggests that despite differences in fractionation schemes and planning techniques, both approaches deliver comparable biological dose distributions to the target.

Radiobiological Parameters

From a radiobiological optimization perspective, the average Tumor Control Probability (TCP) achieved was (90.46 ± 4.61) % for the IMRT HF plans and (95.65 ± 5.52) % for the 3D-CRT CF plans, assuming a fixed α/β ratio of 3 Gy, which is commonly used for prostate cancer. These values highlight a high probability of tumor control in both treatment strategies, with a slight advantage observed in the conventional fractionation approach.

Table 3: Tumour Control Probabilities of the PTV.

Technique	3D-CRT CF Mean (Min-Max, std dev)	IMRT HF Mean (Min-Max, Std dev)
Statistics	95.65(73.79-99.79, 5.52)	90.46 (65.76-97.15, 4.61)
PTV: TCP (%)		

Similar clinical findings were reported by (Dearnaley et al. 2012), who compared a hypo-fractionated (HF) regimen of 60 Gy in 20 fractions with a conventional fractionation (CF) regimen of 74 Gy in 37 fractions, and found comparable efficacy in tumor control. In the present study, 3D-CRT CF demonstrated a slight advantage in average TCP, approximately 5% higher than that achieved with IMRT HF, for localized prostate cancer. This difference may be attributed to the uniform dose delivery from the four equally weighted fields used in 3D-CRT, as opposed

to the modulated intensities in the seven-field IMRT approach, as illustrated by the differences in dose distributions around the target.

Further support for these findings comes from (Mesbahi et al. 2019), who evaluated TCPs for prostate cancer using the EUD model with an α/β ratio of 5 Gy. Their reported TCPs were 98.16% for 3D-CRT and 98.56% for IMRT. When the Poisson model was applied, the TCPs were 97.68% for 3D-CRT and 97.98% for IMRT, reinforcing the idea that TCP outcomes are model-dependent and

sensitive to the $\alpha\beta$ ratio and fractionation scheme used.

These results suggest that no single technique or model universally outperforms the others, and emphasize the importance of further studies to explore how TCP varies across different radiobiological models and treatment strategies. The two extreme data

points in the TCP trends for the 50 patients treated with IMRT HF and 3D-CRT CF (shown in Figure 3) offer valuable insights into patient-specific variability and underscore the complexity of individualized treatment response.

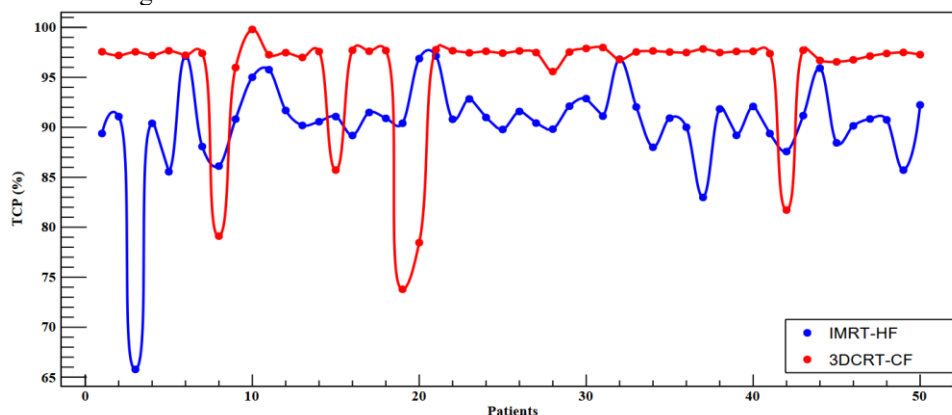


Figure 3: Tumour Control Probabilities achieved using IMRT HF and 3D-CRT CF.

For instance, Patient 3 (as shown in Figure 3), who was treated using the IMRT HF technique, received an Equivalent Uniform Dose (EUD) of 50.45 Gy, resulting in a Tumor Control Probability (TCP) of 65.76%. This suboptimal outcome is attributed to the inverse planning process employed by the Photon Optimizer (PO) algorithm, which adjusted beam intensities to spare the penile bulb, an organ at risk (OAR), that had been contoured within the Planning Target Volume (PTV). Consequently, the optimizer prioritized dose reduction in the overlapping region, leading to underdosage in two CT slices of the PTV. This underdosage is clearly illustrated in Figure 4, which shows the dose distribution of the IMRT HF plan for this patient.

The upper two images in Figure 4 demonstrate that the penile bulb received a

substantial dose in the 3D-CRT CF plan, whereas the lower two images show that the penile bulb was effectively spared in the IMRT HF plan. This contrast highlights a key limitation of relying solely on Dose-Volume Histograms (DVHs) in treatment plan evaluation. Although the DVH for this patient indicated that the overall dose coverage met the clinical acceptance criteria, it failed to reveal localized underdosage within the PTV. Such discrepancies can only be identified through detailed slice-by-slice inspection of the dose distribution. A similar pattern was observed in patient 37, as illustrated in Figure 6, where a portion of the PTV had infiltrated the bladder, a detail that became evident only through direct anatomical visualization in Figure 5.

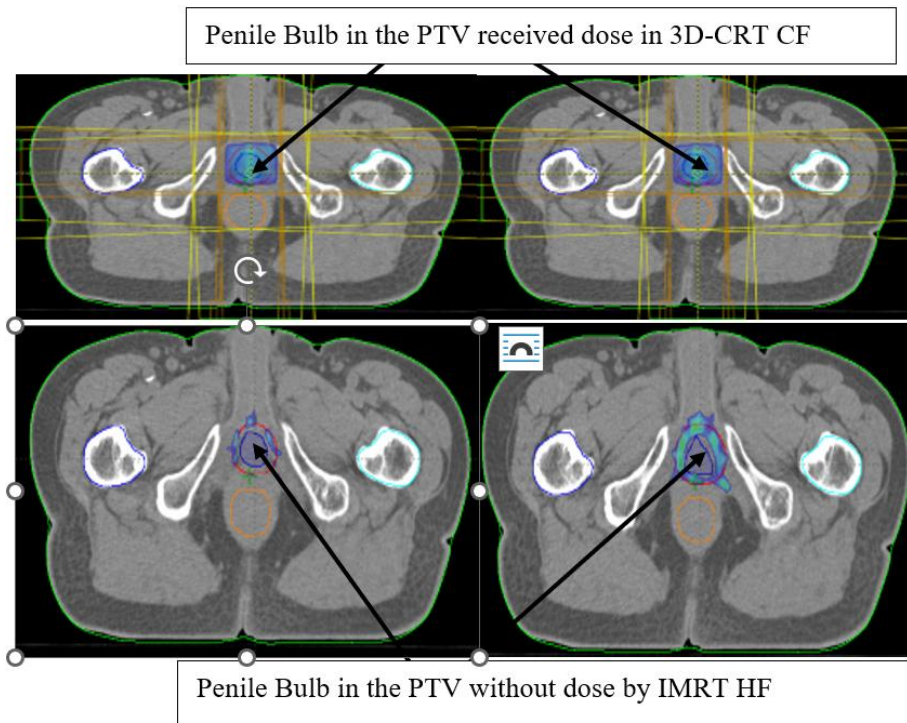


Figure 4: Dose distributions in the penile bulb within PTV by 3D-CRT upper two plans
Two lower plans of IMRT HF.

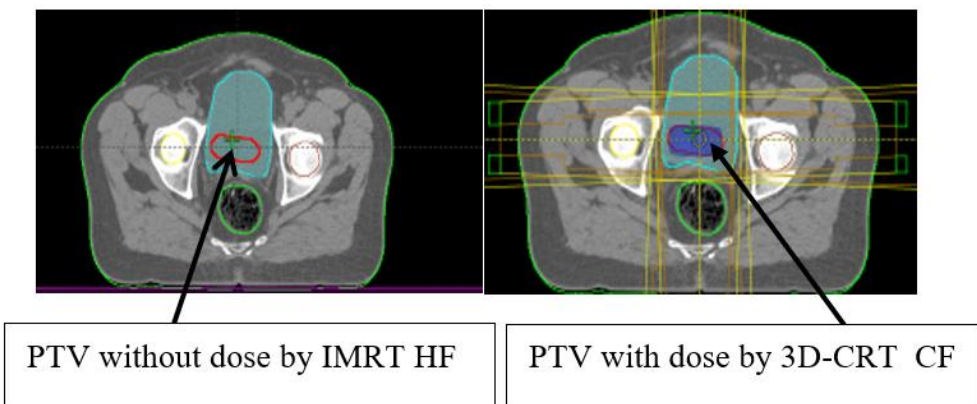


Figure 5: Dose coverage in one of the slices for IMRT HF and 3D-CRT CF.

In Figure 5, the image on the left shows a portion of the PTV that did not receive adequate dose coverage due to the IMRT HF technique sparing the bladder, whereas the image on the right displays the PTV extending into the bladder, which received a higher dose. In both scenarios, underdosage to parts of the PTV resulted in reduced Tumor Control

Probabilities (TCPs). These findings underscore the strong correlation between Equivalent Uniform Dose (EUD) and TCP: as EUD increases, TCP tends to increase, and conversely, lower EUD values are associated with lower TCPs. Moreover, the conventional fractionation (CF) regimen delivering a total of 74 Gy appears to be favored by the EUD

model, yielding higher estimated TCPs compared to the hypo-fractionated (HF) regimen of 62 Gy, as shown in Figure 2. This

trend persists despite the more homogeneous dose distribution typically achieved with IMRT HF plans.

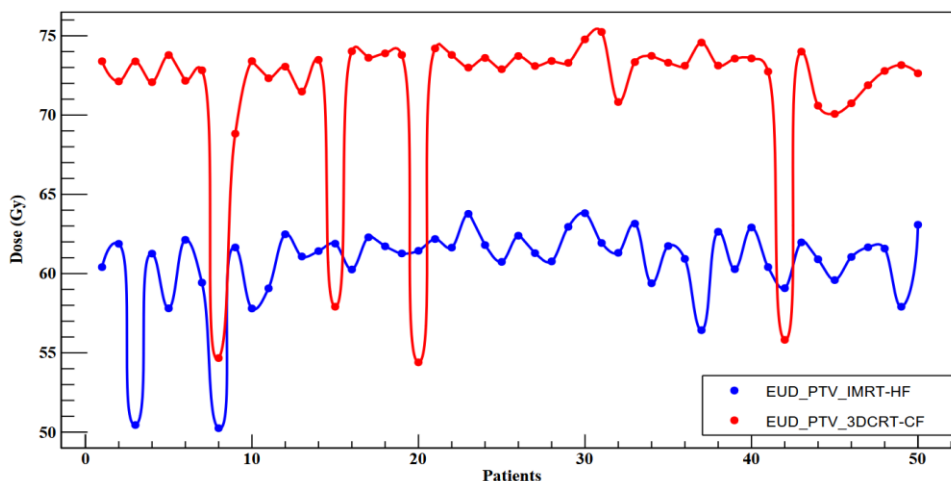


Figure 6: Equivalent Uniform Dose Calculated by EUD model for IMRT HF and 3DCRT CF.

Conclusions

This study demonstrates that 3D-CRT with conventional fractionation (CF) shows a slight advantage, approximately 5% higher TCPs, over IMRT with hypo-fractionation (HF) for localized prostate cancer. The findings address the critical question of whether comparable tumor control probabilities can be achieved using different planning techniques and fractionation regimens. The results confirm that both 3D-CRT CF and IMRT HF can deliver clinically acceptable Equivalent Uniform Doses (EUDs) and TCPs, highlighting the effectiveness of either approach for localized disease when properly planned.

A strong correlation between PTV dose coverage and TCPs was observed, reinforcing the principle that higher dose conformity and uniformity within the target volume directly translate into better tumor control. However, the EUD model used in this study may overestimate TCPs at higher total doses, indicating the need for further validation and comparison with other radiobiological models. Additional clinical investigations are recommended to evaluate the robustness and accuracy of various TCP models across

different fractionation schemes and dose levels.

Declaration of Competing Interest

The authors declare that there is no conflict of interest regarding this work.

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